STUDY ON THE MORPHOPATHOLOGY OF THE NERVES AND NERVE ENDINGS OF LUNG IN TUBERCULOSIS

by

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Introduction

This work is only part of a larger study on nervous lesions in the respiratory tract in different inflammatory diseases and tumors.

In the available literature we were impressed by the great number of works concerning the normal aspects of broncho-pulmonary innervation such as those by A. PLOSCHKO (1897), A. S. DOGIEL (1903), N. P. TISUTKIN (1905), O. LARSELL (1923, 1935), O. LARSELL and DOW (1933), P. SUNDER-PLASSMANN (1933), J. B. GAYLOR (1934), C. DIJKSTRA (1939), G. I. ZABUSOV (1940, 1941), V. F. LASKOV (1938, 1948), I. T. NICULESCU et al. (1952), R. HONJIN (1956) as compared to studies on the pathological aspects of this innervation in different diseases and especially in tuberculosis. The works of A. G. FILATOWA and B. J. LAWRENTJEW (1932), M. L. BOROWSKY (1933), S. S. WAIL (1937), V. F. LASKOV (1938, 1948), O. EMHART (1942), A. T. HAZANOV (1949, 1951), N. E. JARIGHIN (1951, 1956), I. SLEPKOV (1953) and I. M. KOPOLOVA (1958) have brought valuable contributions to this field of pathology but the authors either insist only upon intramural *ganglia* lesions or upon neurovegetative extrapulmonary lesions.

This paper presents the result of our own observations on morphopathology of the nerves and nerve endings in pulmonary structures studied parallel to different tuberculous lesions. The lesions observed in the nerve cells of the intramural vegetative ganglia will be dealt with in another work.

Material and method

This study was carried out on resection specimens from 15 cases of fibrocavitary tuberculosis of the lungs. The evolution of the illness was one year and even more in 11 cases; in the remaining 4 cases the age of the tuberculous lesions could not be accurately determined but was probably much older. All the older identified cases were treated with large quantities of antibiotics.

In each case several fragments of the pulmonary, bronchial and pleural lesions, of the cavity walls, draining *bronchi* and lung close to the macroscopical lesions were studied.

The nervous structures were examined on serial sections by means of TROITSCKY's silver block impregnation.

Specific and non-specific inflammatory lesions were studied on paraffin sections stained by hematoxylin-eosin, van GIESON, WEIGERT for the *elastica* and by GÖMÖRI's method for reticular fibers.

Results

Microscopical study of the cases showed inflammatory lesions associated to pathological aspects of the local nervous structures.

The various inflammatory lesions may be systematised as follows:

— extensive exudative and caseous lesions of the lung encapsulated by productive inflammation and scar-tissue;

— tubercles of the lung, mostly atypical;

— specific and non-specific *bronchitis* with: exudate or *caseum* in the *bronchi*, ulceration, granulation tissue, tubercles with or without typical LANGHANS giant-cells, peribronchial *sclerosis* with *bronchiectasis;*

— specific or non-specific productive *vascularitis* with *sclerosis, stenosis* or obliteration;

— *scleroemphysema;*

— *pleuritis* and pleural *sclerosis.*

The nervous lesions, always present, but with slight differences as to intensity and distribution, were related to the evolutive aspects of the inflammatory non-specific and specific lesions.

Thus we found lesions of the nerves and nerve endings, of the nervous cells in the intramural vegetative *microganglia* (mostly of the irritation type) and of their synapses with preganglionic fibers.

The lesions of the nerves and nerve ending may be grouped in:

— lesions of the nerves and nerve endings of the broncho-vascular formations and *pleura,* in the vicinity of non-specific and specific inflammatory lesions;

— nerve regeneration in the new-growth granulation tissue;

— absence of nerve fibers in scar-tissue.

The lesions of the nerves and nerve endings were especially studied in the main *bronchi* at the level of the *epithelium, chorion,* smooth muscle layer, vessels, isolated nerve fibers and nerves in continuity with intramural *ganglia.* The alternations are mainly found in *bronchi* with ulcerated *mucosa* or parietal lesions. Sometimes they may also be found in the nerve fibers and nerve endings of the intact *bronchi* whose *epithelia* only come into contact with bacilliferous exudates and *caseum* but the most important nervous lesions evidently develop parallel to the more severe bronchial lesions.

Fig. 1. — *Case 2.* Photomicrographs and drawing of the tangential section of a main *bronchus epithelium* close to tuberculous lesions that are not represented here.
The terminal innervation of the bronchial *epithelium* is insured by unmyelinated nerve fibers coming from the *chorion.* These fibers present intense *argentophilia,* are irregularly thickened especially at their ramifications and generally end as relatively coarse argyrophile knobs and sometimes as free nerve endings. The knobs are numerous and may likewise be seen as isolated argentophile masses lying on the bronchial *epithelia.*
TROITSCKY's silver impregnation.

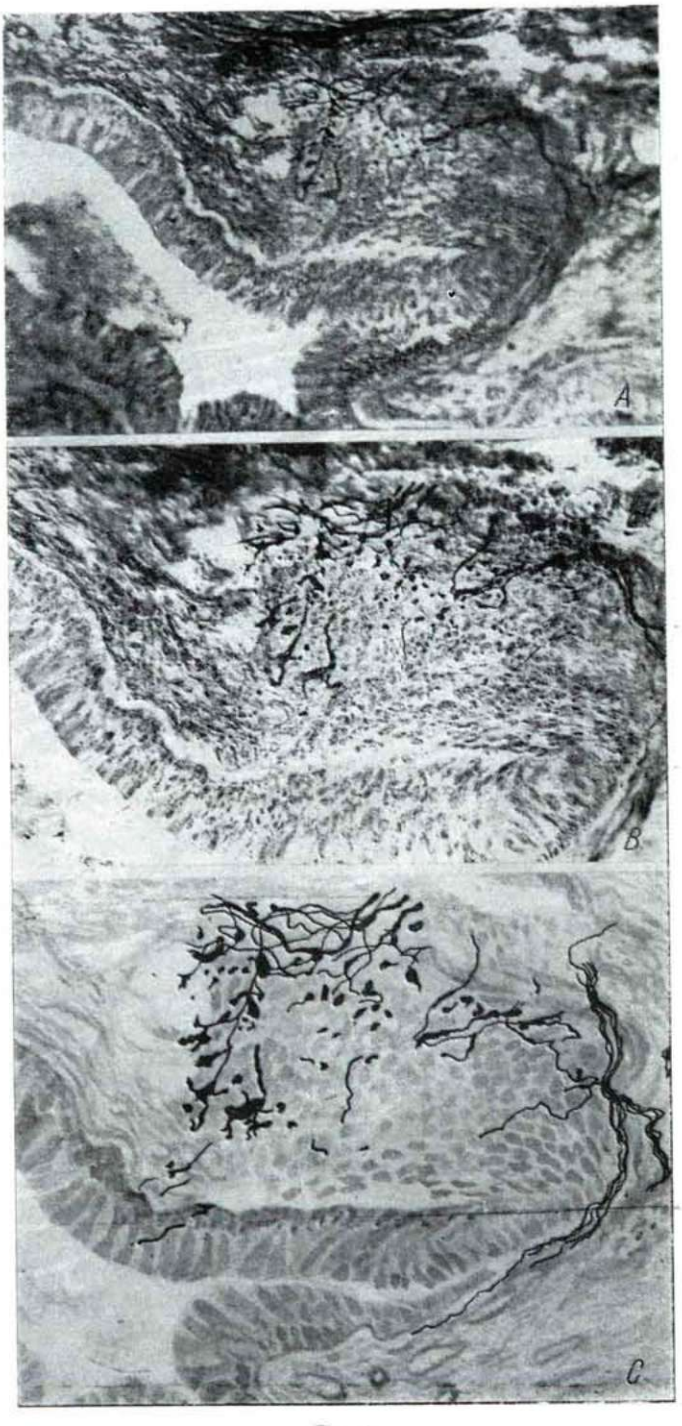

Fig. 1.

Lesions of the sensitive innervation of the bronchial epithelium were found in case 2 (Fig. 1) on tangential sections near exudative and caseous lesions encapsulated by proliferative inflammation.

The isolated unmyelinated nerve fibers originating from the fine nerves of the bronchial *chorion* may be seen on such sections. These fibers lie on the

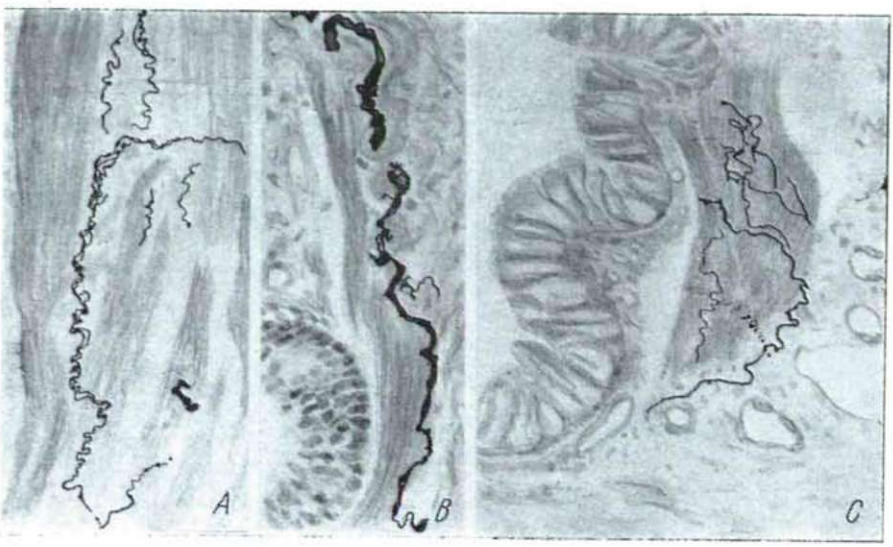

Fig. 2. — *Cases 9 (A, B) and 2. (C).* Drawings of the smooth muscle layer of *bronchi*. *A.* Sensitive innervation fibers with *hyperargentophilia*. *B.* Proprioceptive innervation structure irregularly thickened and with abnormal neurofibril aspects. *C.* Hyperargentophile motor nerve endings, denser than usual.
TROITSCKY's silver impregnation.

bronchial *epithelia* and ensure their innervation. They present intense *argyrophilia,* irregularly distributed fusiform thickenings and varicose aspects. The thickenings are coarser at the ramifications. The nerve fibers mostly end as relatively coarse and irregular sized argentophile knobs and sometimes as free nerve endings. The terminal knobs are so numerous that they may be seen as isolated argyrophile masses lying on the *epithelia.*

In 4 cases in the smooth muscular layer of the *bronchi* wall (Fig. 2) especially in the regions of ulcerated *mucosa,* a sensitive and motor innervation richer than usual with intense argyrophile nerve fibers was found. The more complex proprioceptive formations (normally similar to those of the carotic *sinus* region), also presented irregular thickening and abnormal aspects of their neurofibrils.

The nerve fibers in the bronchial *chorion* are denser than normal (3 cases). On longitudinal and transversal sections of the *bronchi,* the fascicles of fibers proceeding from the numerous nerve stems of the muscular layer, form arcades and end in a richer *plexus,* immediately below the *epithelium* and its basement membrane. On favourable tangential sections (Fig. 3 B, C) one may see a

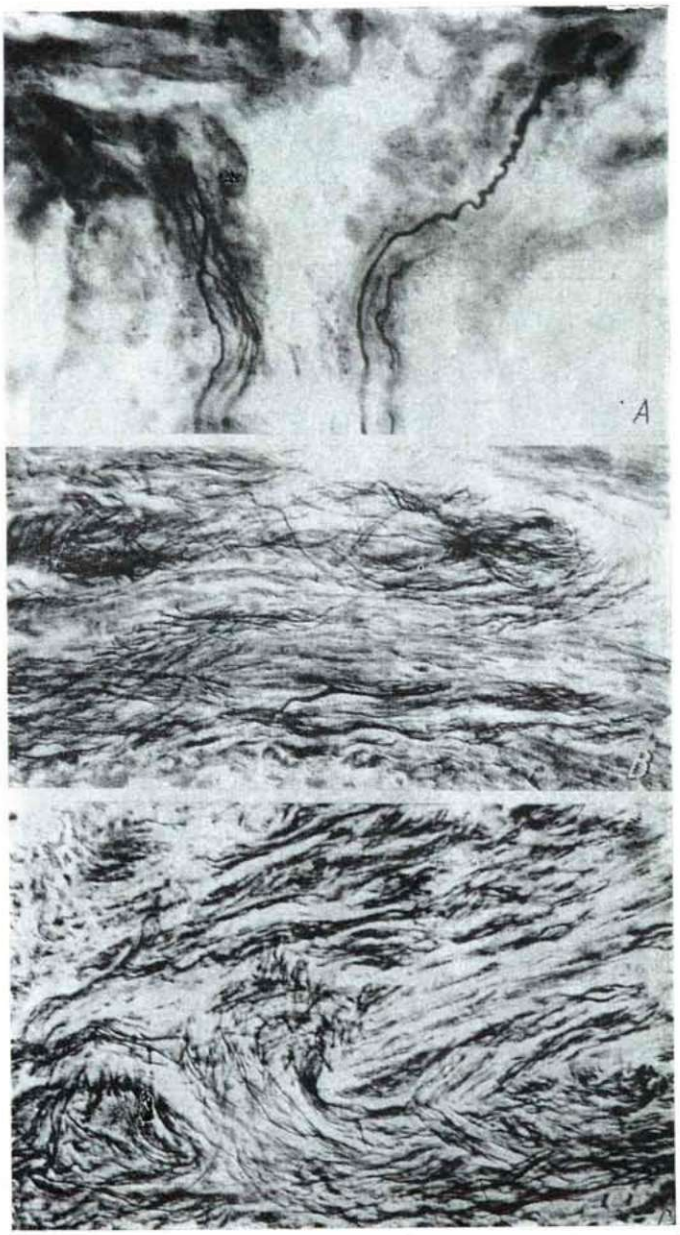

Fig. 3. — *Case 1. A.* Photomicrograph of two nerves on the floor of a tuberculous ulceration in a main draining *bronchus*.
The nerve fibers sprouting from the depth of the bronchial wall show intense *argentophilia*. On the right, one of those fibers presents important differences in size, with varicose aspects, and ends with a hyperargentophile club at ulceration level. *Case 2. B, C.* Photomicrographs of tangential sections of the subepithelial nerve *plexus* of a main draining *bronchus*. There are numerous unmyelinated nerve fibers forming a denser network than normal.
TROITSCKY's silver impregnation.

dense network formed by unmyelinated nerve fibers, of equal size, but presenting relatively intense *argentophilia.*

There is also an increase in the number of nerve fibers of the *adventitia* of the large bronchial and peribronchial vessels, the fibers being more argentophile than usual. These nerve fibers further insure innervation of the arterial *media* according to the normal pattern upon which J. NICOLESCO insisted in his studies on the innervation of the arterial *media.*

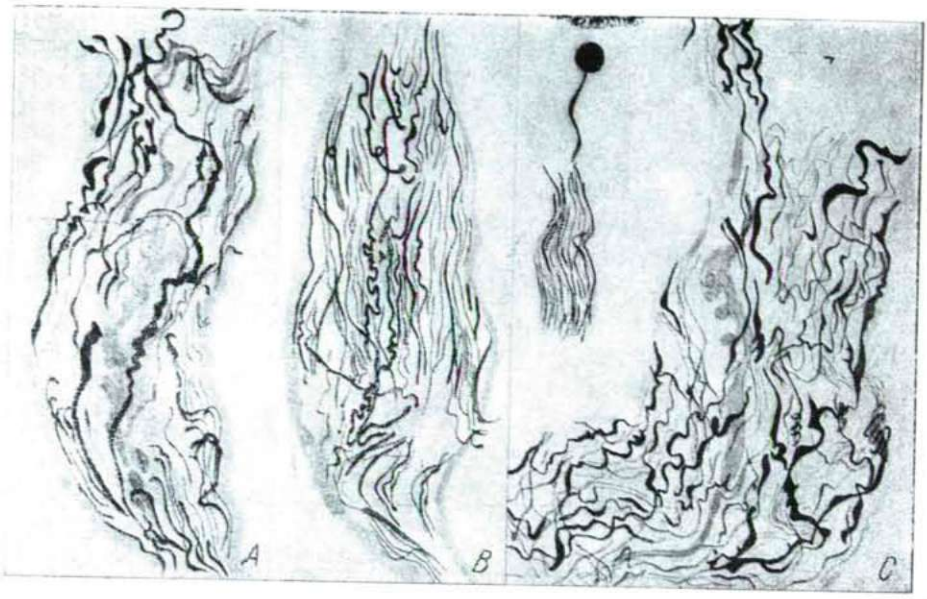

Fig. 4. — Cases 1 (A, B, D) and 5 (C). Drawings of nerves from an ulcerated *bronchus.*
Longitudinal sections of nerves presenting mostly unmyelinated fibers. The axons sometimes present *hyperargentophilia* and inequalities of size with moniliform and varicose aspects. There is a tendency to form spirals. These nerve fibers end in thickened clubs or in a big argentophile ball *(C).*
The myelin sheaths are thickened, of irregular size sometimes showing a tendency to fragmentation.
TROITSCKY's silver impregnation.

The nerves of the bronchial wall frequently present abnormal aspects (Fig. 4, 3 A), more important in the case of extensive parietal and especially ulcerative lesions. Isolated nerve fibers are mostly affected.

The myelin sheaths are irregularly thickened and of moniliform aspect, sometimes fragmented into isolated ovoid globes (7 cases, some with a shorter clinical evolution). These lesions can be localised on part of the myelin sheath only.

Lesions of the axons are less frequent than those of the myelin sheaths. The axons present *hyperargentophilia,* sometimes localised on certain portions of the fiber, fusiform thickenings and varicose aspects. The tendency to form spirals is seldom manifested (2 cases). Especially in the vicinity of ulcerative

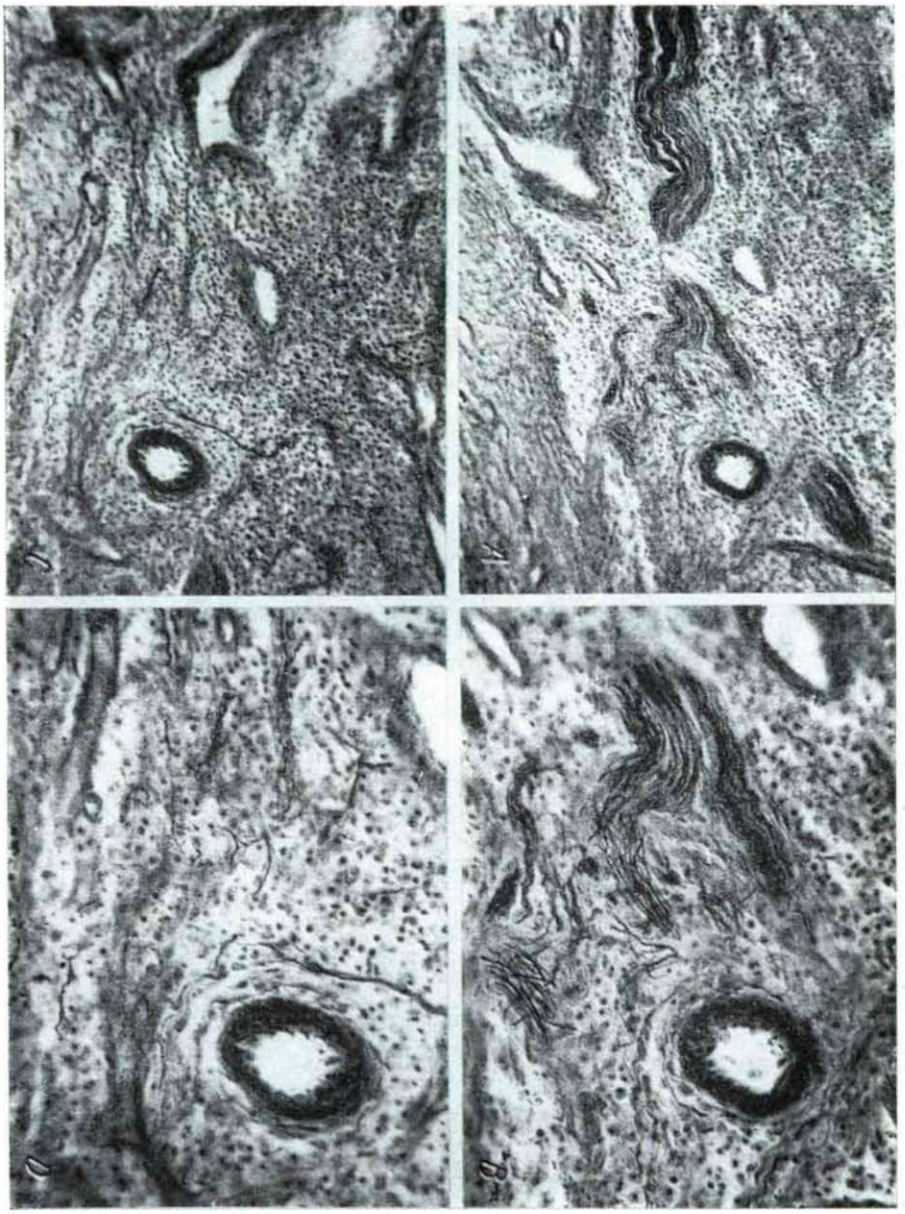

Fig. 5. — *Case 1. A, B.* Sections of an unmyelinated nerve from the wall of a tuberculous cavity.
Isolated nerve fibers sprouting from this nerve insure innervation of a non-specific granulation tissue.
C, D. Serial sections of the same granulation tissue tangential to the nerve from *A* and *B*. At a higher magnification *(D)* one may see the close relationship of the nerve fibers to the new-growth capillaries which they accompany.
TROITSCKY's silver impregnation.

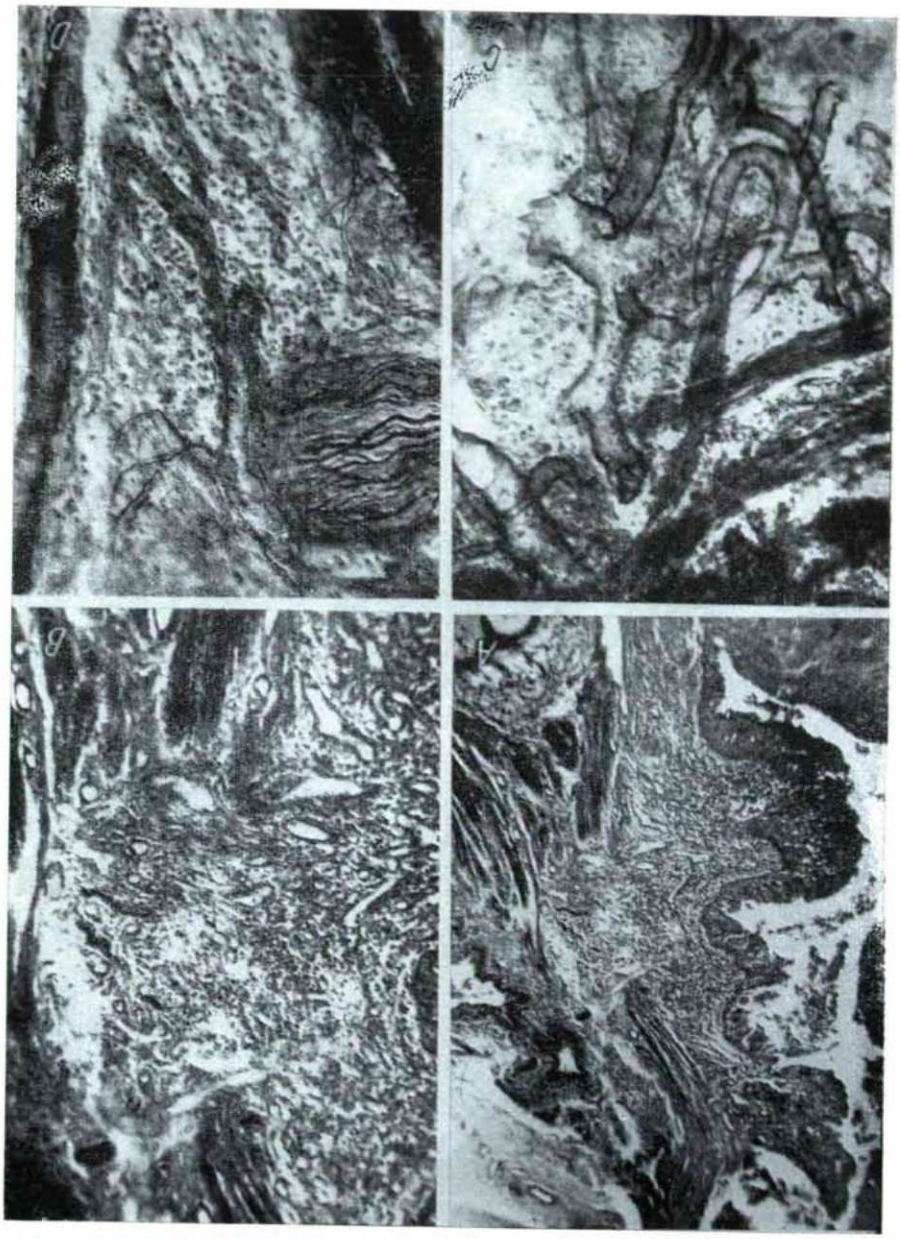

Fig. 6. — *Case 1. A, B.* Photomicrographs of a longitudinally cut main *bronchus* at different magnifications.
The muscular layer of the *bronchus* is interrupted by a nonspecific granulation tissue richly vascularised by new-growth capillaries along which there are also nerve fibers characterised by intense *argentophilia.*
Case 2. C. Photomicrograph of new-growth capillaries from a non-specific granulation tissue. *D.* Nerve fibers originating from a large nerve innervate the granulation tissue; they are hyperargentophile and accompany the blood vessels.
TROITSCKY's silver impregnation.

lesions (Fig. 3 A) and of *sclerosis*, some nerve fibers end (3 cases) as sterile balls (of variable *argyrophilia*), as clubs or as thickened falciform expansions.

In a single case the SCHWANN cells of a bronchial nerve were multiplied with a marked decrease in the number of axons.

Nerve regeneration is frequent in certain stages of tuberculosis.

It is likely that many of the previously described morphological aspects such as greater density of nerve fibers, *hyperargentophilia*, a tendency to form spirals and the ball-phenomenon are also regenerative manifestations.

Nerve fiber regeneration may be asserted for a certainty in the new-growth granulation tissue of the ulcerated bronchial wall, tuberculous cavities and *pleura* (6 cases).

The nerves previously interrupted by inflammatory or ulcerative processes are the origin of isolated regenerated nerve fibers (Fig. 5). These sprout from

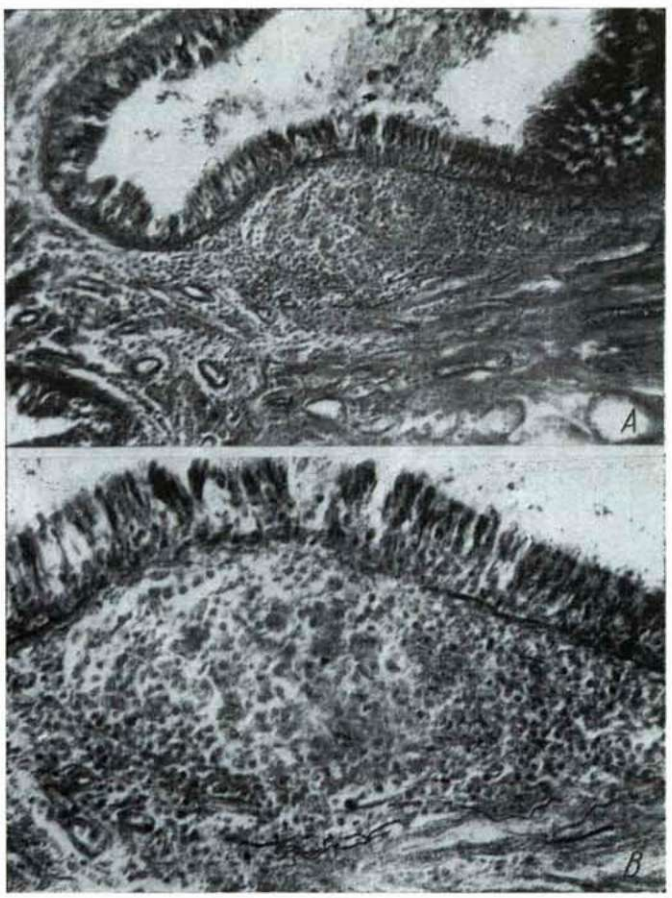

Fig. 7. — Case 1. A, B. Photomicrographs of a tubercle of a small *bronchus* at different magnifications.
There are nerve fibers only at the periphery of the tubercle.
TROITSCKY's silver impregnation.

the interrupted nerve end and form a denser or looser nervous network sometimes recalling the aspects of an amputation *pseudo-neuroma.* Many of the nerve fibers remain in close realtionship to the new-growth capillaries they accompany.

In Fig. 6 the regenerative character of such fibers may readily be determined. A *bronchus* cut lengthwise presents non-specific granulation tissue interrupting the smooth muscular layer. This granulation tissue is rich in new-growth capillaries with their own characteristic morphology and spatial orien-

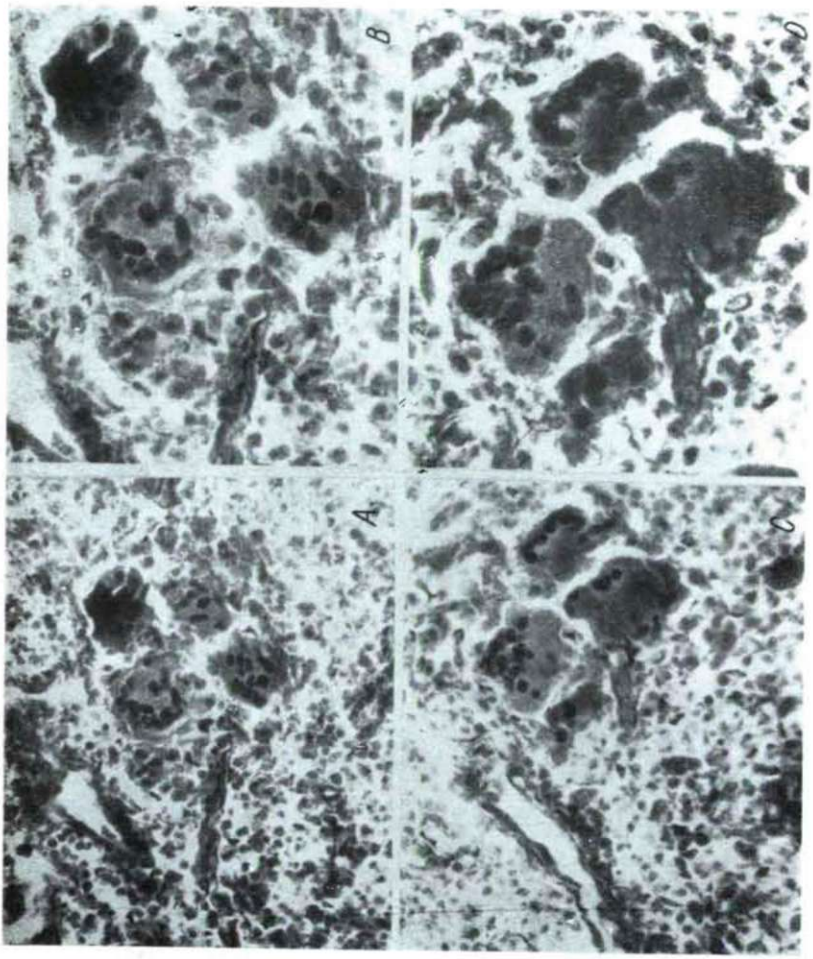

Fig. 8. — *Case 15. A, B.* Photomicrographs of serial sections of a non-specific granulation tissue with giant-cells of endothelial origin from the wall of a draining *bronchus*. Along the capillary vessels from which several giant-cells, actually hypertrophic blind capillary buds, sprout, there are nerve fibers ending at the level of one of these giant-cells *(C, D).*
TROITSCKY's silver impregnation.

tation. The hyperargentophile nerve fibers along these new-growth capillaries thus have the same regenerative significance.

The unmyelinated nerve fibers (Fig. 7) at the periphery of typical and atypical bronchial tubercles (2 cases) may also be considered as regenerated fibers. Their close relationship to new-growth capillaries may be seen on serial sections. The absence of nerve fibers in the center of these proliferating lesions is likewise significant, because the avascular character of tubercles is concidered a characteristic feature of this inflammatory process.

An interesting problem of differential diagnostic may be discussed in case 15 (Fig. 8) where we found regenerated nerve fibers in close connection to the capillaries of a non-specific granulation tissue rich in giant-cells of endothelial origin.

We shall insist upon the regenerative aspects of the nerve fibers of the *intima* of an artery (Fig. 9) situated near the wall of a tuberculous cavity. On multiple serial sections of this vessel (Fig. 10) and its ramifications it was

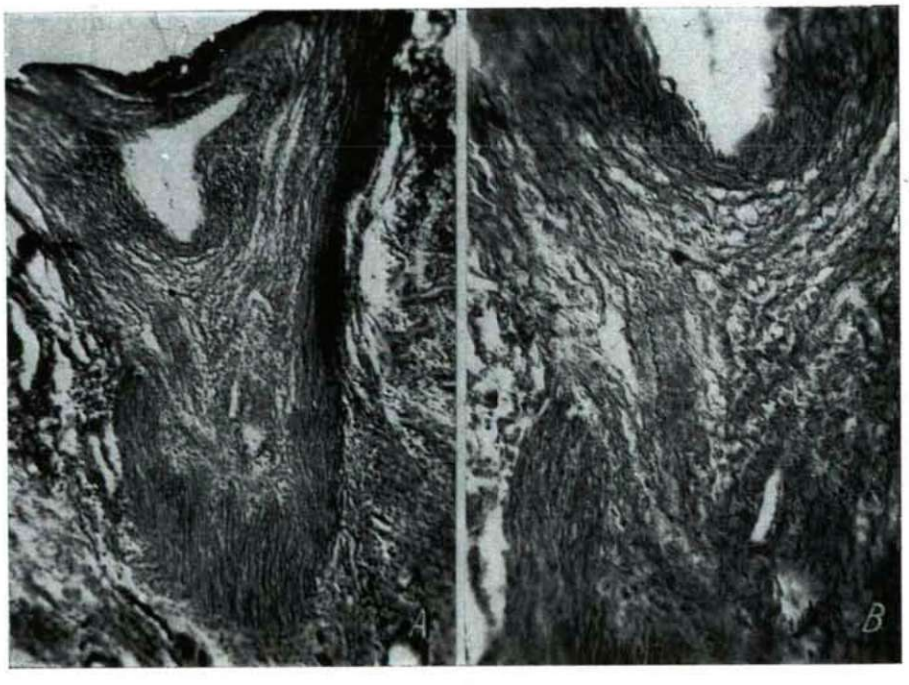

Fig. 9. — *Case 1.* Photomicrographs at different magnifications of the wall of a pulmonary artery situated in the vicinity of a tuberculous cavity.
A. The wall of the artery is much thickened. The proliferated *intima* presents new-growth capillaries and their accompanying nerve fibers. The muscular layer is not modified. The *adventitia* is especially rich in isolated nerve fibers and nerves. *B.* Details at a higher magnification of the nerve fibers within the *intima* in close topographic relationship to the new growth-capillaries along which they advance. Some of these nerve fibers also manifest a tendency to form spirals.
TROITSCKY's silver impregnation.

possible to study the striking parallelism between the parietal proliferating inflammation and nerve fiber regeneration.

In the *adventitia* and in its vicinity there is a non-specific granulation tissue with new-growth capillaries. The smooth muscle fibers of the *media* are not modified but here a pathological vascularisation exists. The blood supply of this sheath and in continuity of the *intima* is insured by new-growth capillaries originating from the adventitial *vasa vasorum*. The *intima* is considerably thickened by intense connective (and also vascular) proliferation. The arterial lumen is irregularly narrowed, even obliterated in the smaller ramifications.

The nerve supply of this artery and its ramifications presents relatively complex morphological aspects. The *adventitia* is very rich in irregularly disposed amyelinic nerve fibers and nerves. Isolated nerve fibers penetrate through the muscular layer of the artery and reach the *intima* along the new-growth capillaries. Because of their topographic relations with the new-growth vessels, their number, *argentophilia* and tendency to form spirals, these intimal nerve fibers have an evident regenerative significance.

The absence of old or regenerated nerve fibers was constant in scar-tissue, especially in the wall of cavities in all the 15 cases studied.

In the granulation tissue in scar-transformation there are aspects of suffering of the nerve fibers, characterized by their rarefaction, changes in *argentophilia* and ball- or club-phenomenon.

The absence of nerve fibers at the level of the scar-tissue may be easily explained when it originates from tubercles, proliferating and avascular processes and therefore devoid of nerve fibers.

Discussion

The nervous lesions presented here have the same characteristics as in 10 cases of different non-specific pneumopathias and cancers studied by us and not yet published. Such nervous lesions cannot be considered as specific, their morphological character being determined only by the duration and intensity of the pulmonary lesions, especially the ulcerative ones. They seem to be secondary to the local lesions.

These nervous morphological aspects may be grouped in degenerative lesions of the nerve endings and nerves (sympathetic and parasympathetic) followed by regenerative processes.

We shall not discuss here the other nervous lesions met with, i. e. primary irritation of the nerve cells of the intramural *ganglia* and transsynaptic modifications of the prepangliar nerve fibers that form synapses with the nerve cells and their dendrites.

Nervous degenerative lesions are constant though relatively discreet in the broncho-pulmonary formations near, or at a distance from the tuberculous lesions. They are encountered in the bronchial nerves, mostly on isolated fibers or segments of fibers and are characterized by lesions of the myelin sheath. These lesions and especially those of its isolated segments may be reversible in the absence of axonal degenerative lesions.

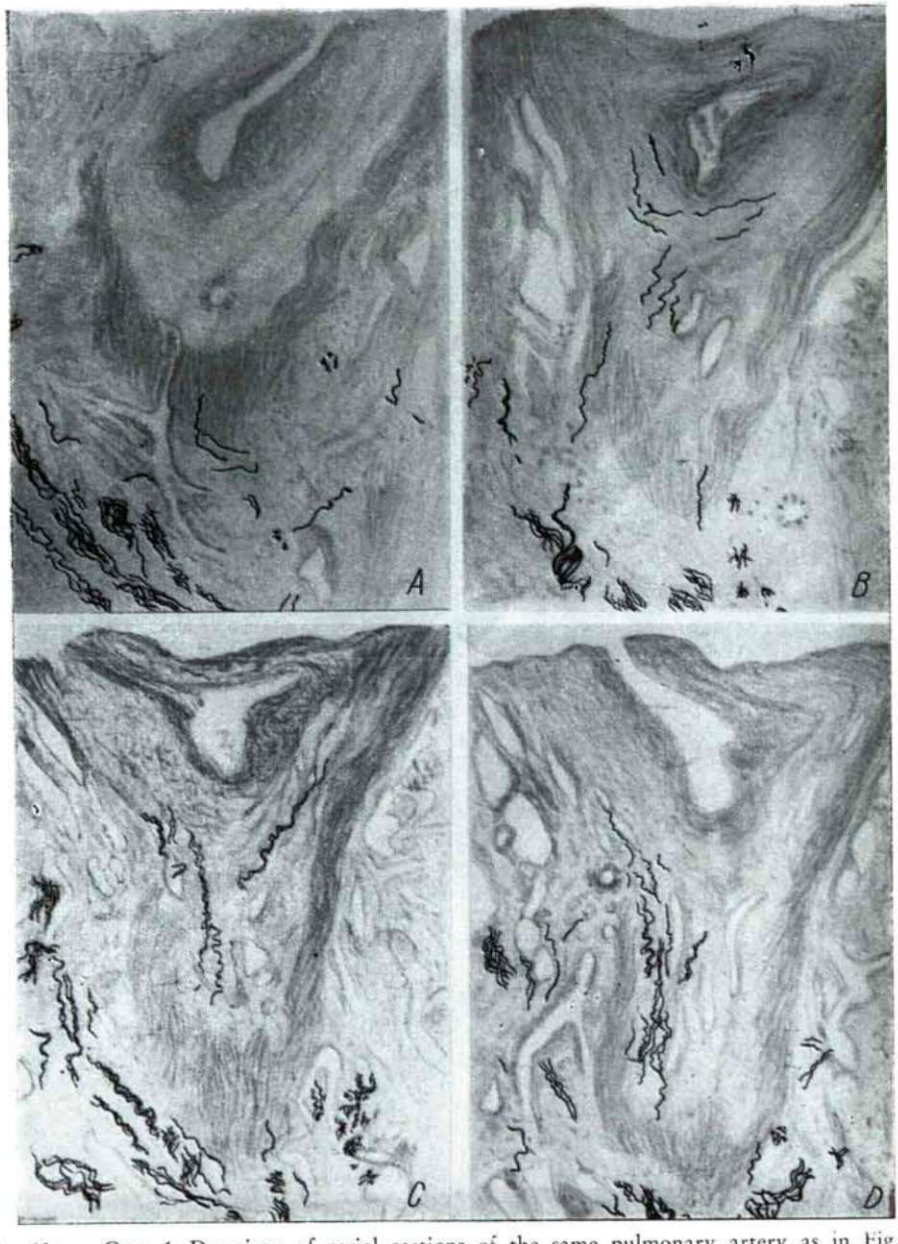

Fig. 10. — *Case 1.* Drawings of serial sections of the same pulmonary artery as in Fig. 9. *A.* The wall of the artery is thickened by intense proliferation of the *intima.* The *intima* and *media* are vascularised by new-growth capillaries sprouting from the adventitial vessels. In the *adventitia* there are also many nerve fiber fascicles and isolated fibers. *B.* Isolated nerve fibers originating from the richly innervated *adventitia* penetrate through the muscular layer of the artery. The intima likewise presents some nerve fibers and new-growth capillaries. *C, D.* The same aspects as in *B* with still more nerve fibers in the *intima.*
TROITSCKY's silver impregnation.

Lesions of the axons are rare. They are followed by regenerative manifestations: *hyperargentophilia*, irregular thickening, tendency to form spirals and ball- or club-phenomenon.

Lesions of the isolated nerve fibers may thus remain without important functional consequences because of the preservation of most of the fibers of these nerves.

The most important degenerative nervous lesions are met with in necrosis and ulceration. They may also be recognized retrospectively by the intensity of nerve regeneration in the new-growth granulation tissue around the necrotic and ulcerative tuberculous lesions.

The absence of the nerve fibers in the scars of the wall of tuberculous cavities, *bronchi*, vessels and *pachypleuritis* is certainly due to previous degenerative lesions of preexistent or regenerated local nerve fibers. It is probable that this denervation has an unfavourable influence on the evolution of non-specific and specific superadded inflammatory processes. This may therefore explain some peculiar aspects of the clinical evolution in many cases of lung tuberculosis.

Nerve regeneration seems to be most frequent in lung tuberculosis.

The pathological aspects described in the nerve endings of the bronchial *epithelium* probably represent an accentuation of the normal phenomenon of permanent regeneration of the terminal innervation at this level, parallel to regeneration of the bronchial *epithelia*. This seems to be a general feature of all the intraepidermal free nerve endings. In this sense, besides evident regenerative manifestations such as *hyperargentophilia*, fiber-thickenings and plain end knobs, the argyrophile masses lying on the *epithelia* are of particular interest as they appear to be the remnants of degenerated end knobs.

The remarkable density of the nervous subepithelial *plexus*, especially at the level of bronchial exulcerations, likewise seems to be of regenerative nature.

The multiplication of sensitive and motor nerve endings in the smooth muscle layer, with their *hyperargentophilia*, and similar modifications of the more complex proprioceptive bronchial nervous formations have the same regenerative significance.

The regenerated nerve fibers of the granulation tissue also represent an important amount of new-growth nerve fibers.

The richness of innervation of the bronchial wall consecutive to regenerative processes could explain part of the pathological reflexes originating from the *bronchi* in lung tuberculosis. Classical researches likewise insisted upon the morphological similarity of nerve regeneration and nerve growth processes (CAJAL) and upon the local abundance of enzymes (oxydases — in fact *c-cytochromoxydase* — identified by SCHULTZE's reaction by G. MARINESCO). Such facts have not lost their present day interest. They are of importance because they indicate that apart from the increased number of nerve fibers the character of their function may also suffer modifications especially at the level of the abortive forms of regeneration such as sterile end balls and clubs.

We should like to emphasize the regenerative significance of the multiplication of nerve fibers in the sheaths of certain pericavitary arteries and especially within the *intima*.

Previously, one of us (ST. N.) studied the relationship between vascular lesions in lung tuberculosis and the frequency of right heart terminal insufficiency in certain cases of extensive fibro-cavitary tuberculosis. The presence of the regenerative *intima* nerve endings in the lung arteries seems to be a morphological argument lending support to the existence of a neuroreflex mechanism that contributes to hypertension in the pulmonary circulation in fibro-cavitary tuberculosis besides arterial *stenosis* and obliteration due to inflammatory and sclerous processes. But the exact importance of this *neuroreflex factor* seems to be hard to determine because identification of the *intima* nerve endings is technically difficult. It is also probable that in the following stage of *intima sclerosis* the regenerated nerve fibers, compressed by connective fibers, disappear.

The great number of regenerated nerve fibers in the pleural granulation tissue may also explain the pain symptoms so frequent in pleural pathology.

In conclusion, stress may be laid on the importance of lesions of the nerves and nerve endings in the lung in tuberculosis, their relation to local inflammatory lesions and possible influence on the course of the clinical evolution and complications of this illness. It seems likely that many of the clinical manifestations of lung tuberculosis will be explained by increasing knowledge in this field of nervous pathology.

Summary

A histopathological study of the nerves and nerve endings in the respiratory tract in fibro-cavitary tuberculosis is presented. The nervous lesions were studied in 15 cases by means of TROITSCKY's silver block impregnation in correlation to the various inflammatory specific and non-specific lesions identified by current methods.

1. Non-specific nervous lesions of degenerative and regenerative character were identified at the level of the various broncho-pulmonary and pleural inflammatory lesions and also at a distance.

2. The *bronchi* present: abnormal aspects of the terminal innervation of their *epithelium, chorion* plexuses, smooth muscle layer, bronchial nerves and neurovegetative *microganglia*. In the non-specific granulation tissue regenerated nerve fibers are to be found in close relationship to new-growth capillaries. The nerve fibers are absent in the central part of bronchial tubercles and in scar-tissue.

3. The *pleura* shows nervous regenerative aspects at the level of the non-specific granulation tissue. The nerve fibers are absent in the pleural scar-tissue.

4. The arteries situated in the immediate vicinity of a tuberculous cavity present in one case a productive non-specific inflammation and regenerated *intima* nerve fibers in close connection to the new-growth capillaries originating from the *vasa vasorum*.

5. The importance of bronchial nerve and nerve ending lesions is emphasized in relation to the pathological reflexes originating from the *bronchi*

during chronic tuberculosis. The existence of the regenerated intimal nerve endings in the pericavitary arteries is a morphological argument for a neuro-reflex mechanism in the appearence of right heart failure in fibro-cavitary tuberculosis, besides arterial *stenosis* and obliteration due to inflammatory and sclerous processes.

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